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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,098	10/14/2004	Akira Ideno	Q83564	9139

23373 7590 01/18/2008

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

MAIL DATE	DELIVERY MODE
01/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,098	IDENO ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-64* is/are pending in the application.

4a) Of the above claim(s) *38,39,43-52,57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-37,40-42,53-56 and 59-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/07, 9/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 1-32 have been canceled. Claims 33-64 are at issue and are present for examination.

Claims 38, 39, 43-52 and 57-58 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/23/07.

The amendment to the claims filed on 11/9/07 does not comply with the requirements of 37 CFR 1.121(c) because it does not indicate those claims withdrawn by the correct identifier. Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) which states:

> (c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

Furthermore, applicants citation of paragraph numbers from the published application to indicate support for amendments to the claims is confusing and makes examination difficult as the

paragraphs of the original application are not numbered, and the examiner has to locate the citation in the original specification not in the published document. It is requested that all future recitations of specification positions refer to page and line numbers of the original specification and not to paragraph numbers from the published application.

Claim 60 is objected to because of the following informalities: "a host" should be "the host cell" in view of the amendments to claim 59 from which claim 60 depends. Appropriate correction is required.

Claims 35 and 59-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is confusing in the recitation of an "expression vector of claim 33" … "encoding a protease digestion site in the same reading frame as the first and second coding regions." as the expression vector of claim 33 does not in fact include a second coding region but merely a restriction site into which a second coding region may be inserted. It is suggested that "the first and second coding regions" be replaced with "the first coding region". The examiner regrets that she in fact suggested the confusing language.

Claim 59 (upon which claims 60-64 depend) is confusing in the recitation of "A process for producing a fused protein" … "comprising culturing a host cell transformed with an expression vector of claim 33" as the vector of claim 33 does not include a second coding region fused to the first coding region but merely a restriction site into which a second coding region may be inserted. It is suggested that this claim be made dependent on the vector of claim 36 (as it was previously) which includes the second coding region.

Claim 60 is confusing in the recitation of "under condition of expression of the expression vector, and expressing the fused protein in a cytoplasm" as this recitation is grammatically awkward and confusing. It is suggested that this be replaced with "under conditions suitable for expression of the expression vector to produce the fused protein in the cytoplasm of said host cell".

Claim 61 is unclear in the recitation of "a signal sequence at … a 3′ terminus of the second coding region" as signal sequences which provide for export into the periplasm or media when fused at the 3′ terminus of a protein coding sequence are not known in the art.

Claim 61 is confusing in the recitation of "under condition of expression of the expression vector to express the fused

protein in the periplasm or a medium" as this recitation is grammatically awkward and confusing. It is suggested that this be replaced with "under conditions suitable for expression of the expression vector to produce the fused protein in the periplasm of said host cell or medium of said culture".

Claim 62 is confusing in the recitation of "culturing a host cell transformed with the expression vector to express the fused protein in a cell-free translation system" as it is unclear how culturing a host cell can be accomplished in a cell-free system. A cell free system inherently excludes the presence of an intact cell. It is suggested that this claim be replaced with an independent claim reciting production of a fused protein by a method comprising in vitro transcription and translation of the expression vector of claim 36 in a cell-free system.

Claim 63 is confusing in the recitation "carrier harboring macrolide, cyclosporine …" as it is unclear if harboring is synonymous with "bound or conjugated to" or encompassed something else also.

Claim 64 is confusing in the recitation of "which comprises digesting the fused protein comprising the protease digestion site obtained by the process according to claim 59, with a protease digesting a protease digestion site" as there is no

protease digestion site in the expression vector of claim 33 (recited in claim 59) and it is unclear as written that the protease used must cleave the protease digestion site present in the fused protein. It appears that the lack of clarity arose here due to confusion by applicant regarding the previous suggestion to change the phrase "a protease digestion site" in claim 64 to "the protease digestion site". The examiner did not realize when she made the suggestion that the phrase appeared twice in the claim and applicants inadvertently changed the wrong one. It is suggested that the claim be amended to recite "which comprises digesting the fused protein comprising a protease digestion site obtained by the process according to claim 59, with a protease digesting the protease digestion site".

Claim 61 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as filed does not provide support for the recitation of "a signal sequence at … a 3′ terminus of the

second coding region". Applicants cite to pages 24 and 26-28 of the original specification for support for the instant amendment but nothing on any of these pages discloses the presence of a signal sequence at the 3' terminus of the second coding region. Furthermore, no such signal sequences are known in the art. Signal sequences for secretion of a protein are commonly found at the 5' terminus of the protein.

Claims 33-37, 40-42, 53-56, and 59-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is explained in the previous Office Action.

Applicants argue that prior to the filing date of the present application, nucleotide sequences encoding, and amino acid sequences for, PPIases were known in the art and that applicants need not teach what is known to the art. However, while the examiner acknowledges that the art teaches the structures of several PPIases, these known PPIases are clearly not representative of the structure of any PPIase as is currently claimed. The term PPIase is extremely broad including

any protein having petidyl-prolyl cis/trans isomerase activity. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Since the genus of PPIases encompasses any protein whether naturally produced or synthetically made by man having any possible structure at all and there are enormous numbers of different structures which impart petidyl-prolyl cis/trans isomerase activity, the PPIases provided by the art and/or the specification are clearly not representative of the structure of any PPIase.

Claims 33-37, 40-42, 53-56, and 59-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expression vectors comprising a sequence encoding PPIase from *Methanococcus thermolithotrophicus*, *Thermococcus* sp. KS-1, *Methanococcus jannaschii*, *Methanosarcina mazei*, *Methanosarcina acetivorans*, and *Methanosarcina barkeri* and uses thereof, does not reasonably provide enablement for expression vectors comprising a sequence encoding any PPIase having molecular chaperone activity and methods of use thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is explained in the previous Office Action.

Applicants argue that the examiner relies on In re Fisher, 166 USPQ 19 24 (CCPA 1970) and In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) to support the instant rejection and that the facts of this case are not like those of In re Fisher but that the present facts resemble those under review in In re Wands, wherein the Court reversed the Examiner's rejection for lack of enablement holding that undue experimentation would not be required to practice the invention because it is known that in producing antibodies it is routine to first make

monoclonal hybridomas to determine which hybridomas secrete antibodies with the desired characteristics. However, the examiner cited the instant cases not to argue that the fact patterns were the same but merely to provide a citation for the statement that law requires that the scope of the claims must bear a reasonable correlation with the scope of enablement (Fisher) and to provide a citation for the factors which are considered during a enablement decision (Wands). To the extent applicants are arguing that in the instant case as in Wands it is routine to make mutant proteins of a known protein to determine which have the desired characteristics and that thus the scope of the current claims is enabled this is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., encoding a PPIase) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine

screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting PPIase activity; (B) the general tolerance of PPIases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any PPIase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Applicants further argue that because the enablement rejection is grounded in limitations not recited by the claims (e.g., mutant PPIases), it appears the specification and claims were not duly considered prior to issuance of the outstanding Office Action. However, this is simply an untrue statement. The rejection discusses enablement of mutant PPIases because the claims are not limited to the known PPIase proteins. The examiner is required to consider the full scope of the claims not just those embodiments made by applicants.

Claim 55 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell transformed with the recited expression vector, does not reasonably provide enablement for host cells within a multicellular organism that have been transformed with the recited expression vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 55 is so broad as to encompass host cells transformed with a specific expression vector, including cells in *in vitro* culture as well as cells within any multicellular organism. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of host cells broadly encompassed by the claims. While methods for transforming cells *in vitro* are well known in the art, methods for successfully transforming cells within complex multicellular organisms are not routine and are highly unpredictable. Furthermore, methods for producing a successfully transformed cell within one multicellular organism are unlikely to be applicable to transformation of other types of multicellular organisms as multicellular organisms vary widely. However, in this case the disclosure is limited to only host

cells *in vitro*. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of host cells within a multicellular organism for the production of polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, expression of genes in a particular host cell and having the desired biological characteristics is unpredictable the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is suggested that applicants limit the claim to "An isolated host cell …".

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 33-37, 53-56, 59-62, and 64 rejected under 35 U.S.C. 102(a and e) as being anticipated by Scholz et al. (US PG-PUB 2003/0096352).

Scholz et al. teach expression vectors for producing a fusion protein comprising a chaperone polypeptide which is a PPIase fused in frame to a protein of interest. Preferably the chaperone polypeptide is *E. coli* FkpA, SlyD or trigger factor which are FKBP-type PPIases. (see paragraphs 13, 14, 32, 41, and 42). Scholz et al teaches that suitable proteins of interest include antibodies and membrane proteins (see paragraph 38). Scholz et al. further teach the inclusion of a suitable restriction site for insertion of the sequence encoding the protein of interest following the chaperone polypeptide (see paragraph 50), sequences encoding a protease digestion site between the chaperone polypeptide and the protein of interest (see paragraph 50 and 64) and inclusion of a signal sequence preceding the chaperone polypeptide encoding region for the secretion of the fusion protein (see paragraph 38). Scholz et al. further teach that the expression vectors may be used to express the fusion protein in a cell-free translation system (see paragraph 66). As such Scholz et al. anticipate all of the instant claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-37, 40-42, 53-56, and 59-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fersht (WO 00/75346) in view of Furutani et al. The rejection is explained in the previous Office Action.

Applicants argue that Ferscht et al. does not teach each and every element of Applicants invention because Ferscht et al. disclose a vector having a first coding region encoding a fragment of a chaperone but the 191-345 GroE1 fragment does not have molecular chaperone activity. Applicants argue that Ferscht et al. do not suggest nor motivate one skilled in the art to use a chaperone fusion protein in order to obtain soluble proteins. However, this is not persuasive as chaperone activity is NOT defined as the ability to produce a protein in soluble form nor do applicants claims require that the fusion protein be produced

in soluble form. Page 8 of the specification states that chaperone activity means activity of re-folding a denatured protein into an original natural type, or activity of inhibiting irreversible aggregation of a denatured protein. Ferscht et al. define chaperone fragments as disclosed in that reference similarly. Page 8 of Ferscht et al. states that chaperone fragments as referred to herein, is any fragment of a molecular chaperone which possesses the ability to promote the folding of a polypeptide in vivo or in vitro. Preferred fragments are described in International patent application WO98/13496, incorporated herein by reference. Especially preferred are fragments 191-375, 191-345 and 193-335 of GroEL. WO98/13496 clearly show that GroEL 191-345 has activity to refold cyclophilin. Thus Ferscht et al. clearly do teach a vector having a first coding region encoding a fragment of a chaperone that has molecular chaperone activity as defined by the instant specification.

Applicants further submitted a 1.132 declaration of Dr. Ideno which compares the expression of Applicants' TcFk fusion 2 system to the expression in the GroEl (191-345) fusion system of Fersht et al. While this declaration might be sufficient to show unexpectedly superior results of applicants exemplified system to one embodiment of the system of Ferscht et al., any

showing of unexpected results is clearly not commensurate in scope with the claimed invention. Applicants claims are not limited to the TcFk fusion 2 system used and different fusion partners are likely to produce very different results. As such the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
Art Unit 1652